Catching up in pharmaceuticals: a comparative study of India and Brazil

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Abstract

Since the mid-twentieth century, the national objective of India and Brazil has been to develop industrial capabilities in essential sectors such as pharmaceuticals. At the outset, they shared some common features: a considerable period of lax intellectual property rights regimes, large internal market and a reasonably strong cadre of scientists and engineers. However, over fifty years, India has had much more success in building indigenous capabilities in pharmaceuticals than Brazil, at least to date. Why? In exploring the answer to this question, we show that in both countries the design of State policy played a crucial role and the endogenous responses in the national system of innovation consisted of two parts. On the one hand, most of the time, the predicted and desired outcome was partially realized and on the other hand, there were invariably, other unpredicted responses that emerged. The latter unexpected elements, which were specific to the two countries, pushed them along distinctive trajectories.

Keywords: Pharmaceutical industry, India, Brazil, industrial capabilities, Catch-up.

JEL codes: O330, O380, O570.

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1. Introduction

Taking off with the discovery of antibiotics, the pharmaceutical industry emerged as a distinct sector in the developed world in the last century, when research and development (R&D) activity by firms greatly increased in order to find solutions to the problems and demands created by the two World Wars. Since then, it has continued to be a highly R&D intensive industry with technological competencies and innovation creation being important determinants of firm survival and growth. Such trends were reinforced with the emergence and integration of biotechnology during the 1980s[1] and the commercial success of radical innovations such as recombinant insulin, human growth hormone, interferon, TPA, EPO etc (Achilladelis and Antonakis, 2001; Malerba and Orsenigo, 2002)[2]. Major innovators of the pharmaceutical industry are to be found only in five countries: USA, Germany, Switzerland, the UK and France, where they were greatly supported by favorable national policies in terms of public and private research (McKelvey and Orsenigo, 2001). Nevertheless, some emerging economies have developed significant industrial capabilities over the last 50 years. The objective of this chapter is to unravel the determinants of the catching-up process of this group through a case study of two such countries: India and Brazil.

India and Brazil are interesting countries to compare because they share some common features. Since the mid-twentieth century, the national objective of both these countries has been to develop industrial capabilities in essential sectors. The two countries also enjoyed a considerable period of lax intellectual property rights (IPR) regimes, when product patents were not allowed in the pharmaceutical sector. Both countries are very large and have a reasonably strong cadre of scientists and engineers. However, over fifty years, India has had much more success in building indigenous capabilities in pharmaceuticals than Brazil, at least to date. Why? Are the different patterns of catching-up related to differences in the accumulation of capabilities by domestic firms and their strategies? If yes, what explains these differences? These are the questions we intend to explore in this chapter.

Pharmaceutical products of today broadly fall under one of three types: drugs, vaccines and diagnostics. For the purposes of this paper, we focus only on drugs and refer to industrial capabilities as the capacity of domestic firms to satisfy national and international demand in terms of the quantity, quality and variety of drugs locally produced. We further consider industrial capabilities to include two components: manufacturing capabilities and innovation capabilities.

[1] Biotechnology refers to techniques that involve manipulation or change in the genetic patrimony of living organisms. They emerged from advances in the life sciences from the mid 1970's.

[2] For instance between 1980 and 1990 the radical innovations to be commercialized were: Insulin (by Eli Lilly in 1982); Human growth hormone (by Genentech in 1985, Eli Lily in 1987, Novo-Nordisk in 1988, Ares-Serono in 1988, Biotechnology General in 1989); Alpha 2 interferon (by Schering Plough in 1986, Hoffman La Roche in 1986); Monoclonal Orthoclone OKT3 (by Ortho biotech in 1986), Tissue Plasminogen Activator TPA (by Genentech in 1987), Erythroprotein EPO (by Amgen in 1989), Hepatitis B vaccine (by Smith Kline and Beecham in 1989).

The manufacturing of drugs involves three main operations and the associated capabilities are different in terms of technological complexity. The least complex step is 'formulation' of drugs, which refers to the processing and packing of the basic ingredients called 'bulk drugs' into a consumable form such as a tablet, capsule, syrup, injection, plaster, etc. The production of 'bulk drug' containing the therapeutic molecule in powder or liquid is a more complex process requiring a higher level of scientific and technological capabilities. But the most complex step is to produce the core component of bulk drugs termed the 'active pharmaceutical ingredients' (or API).

In defining innovation capabilities, we distinguish between 'reengineering skills' and 'new drug discovery skills'. Usually a late-comer country firm starts by building reengineering skills i.e. by independently developing new processes to produce copies of existing drugs. Once a firm learns to manufacture bulk drugs and eventually API, it can envisage investing in the development of 'new drug discovery capabilities'. Capabilities in new drug discovery can take the form of integration of biotechnology and/or research capabilities in one or more of the steps in the new drug discovery process. To date, no developing country firm has patented a new chemical entity.

Furthermore, developing country firms have to build up complementary competencies that go beyond technology, if they want to commercialize drugs. The regulatory procedure to commercialize a copy of a branded drug is relatively simple. Firms just need to submit proof of their chemical and therapeutic equivalence with the proprietary drug; though some additional information and technical support need to be provided to the regulatory authority to enter the market and such requirements vary from country to country. On the other hand, to commercialize a new drug, data has to be generated on preclinical tests on animals followed by a 3-phase series of clinical testing on human beings, at the end of which a new drug application can be made with the concerned regulatory authority. At present, very few developing countries have a patent or regulatory bureaucracy that can deal with an application for the commercialization of a new proprietary drug, especially if it involves biotechnology.

At this point, before continuing further, we would like to highlight three caveats. First, we focus in what follows on how India and Brazil built their pharmaceutical industries. However, such an analysis cannot be used to draw any conclusions on whether or not a lower or middle income country should invest in the creation of manufacturing or innovation capabilities. There are many countries with manufacturing capacity in formulations and limited or no competence in the production of bulk drugs, which still rely on imports to satisfy their demand. And there are also countries, mainly in Africa, which have no manufacturing capacities and are totally dependent on imports of drugs. Improvement of the health status of its citizens is a common objective of all countries, but the way it is to be done – whether through investment in the creation of manufacturing capabilities, investment in a national health care system or provisions for health insurance – is a national prerogative, to be determined by policy makers, as a function of the country's specific demographic, institutional, economic and geopolitical realities.

Second, caution must be exercised in drawing conclusions on the role of IPR in the catching-up process of developing countries from our case studies. Catching up through copying, i.e. developing re-engineering capabilities, was indeed the traditional route pursued by most

developed countries (including the USA) to build manufacturing and innovation capabilities in their knowledge intensive sectors in earlier centuries (OTA, 1986). This was possible because the Paris Convention of 1883, followed by most countries till the end of WWII, gave freedom to the signatories to set up their own IPR systems, according to their nation's individual needs. Thus, nations with a technological retard usually chose to have a loose IPR regime with process rather than product patents during their period of catching up. At the same time, clearly, the accumulation of innovation capabilities does not depend only on the prevalent IPR regime, being a function of a number of complementary factors such as the resource base and the scientific, industrial, innovation and social capabilities of a country (Fagerberg and Godinho, 2004; Abramovitz, 1986). Therefore, the results that we present and discuss in this paper on India and Brazil cannot be used to formulate policy recommendation for another country without consideration of the possible interactions between the IPR regime and other country-specific factors and geopolitical constraints.

Third, catching-up in pharmaceuticals has been made more complex since 1995 with the creation of the World Trade Organization (WTO) and the international homogenization of IPR regimes. The 'Trade Related Intellectual Property Rights' agreement (TRIPS), signed by all member countries of the WTO, imposes product patents in all sectors, including pharmaceuticals. Under this new international legal framework, branded drugs cannot be re-engineered except under specific conditions. This means that catching up via the accumulation of re-engineering capabilities is still possible only for drugs whose patents have expired. The impact of TRIPS on the future trajectories of countries committed to a catching-up process in pharmaceuticals cannot be deduced from our case studies. This will depend on a host of other factors such as the understanding of flexibilities embedded in TRIPS, the functioning of the regulatory bureaucracy, the engagements of the country in bilateral agreements (TRIPS+ agreements) and geopolitical constraints.

The methodology adopted in the present paper is that of the 'national systems of innovation' (NSI) approach, which has emerged as a useful framework to study the 'catching-up' process of countries (Lundvall, 1992; Nelson, 1993; Freeman, 1995; and Edquist, 1997). It provides a useful tool to organize historical evidence on the building of different capabilities. The NSI structure has also been refined along a number of dimensions such as sectoral specificities (Malerba, 2002) and features of developing countries (Rodrigo and Sutz, 2000), both of which are incorporated in the present chapter.

The rest of the chapter is organized as follows. Section 2 examines the process of catching-up in India, followed by section 3 which traces the evolutionary trajectory of Brazil. Then section 4 identifies the major differences between the two trajectories and proposes explanations for the same. Section 5 concludes with further insight on catch-up theories and policy recommendations.

2. India[3]

When India attained its independence in 1947, its pharmaceutical industry was of a very modest size with market sales of about $28.5 million (Ahmad, 1988). Western multinationals (MNCs) held about 80% of the market with the remainder being served by several Indian owned companies operating on a much smaller scale. No Indian company had manufacturing capabilities in either bulk drugs or formulations. There was heavy dependence on imported drugs, which were marketed directly by the MNCs established in India and local agents of MNCs that did not have a local presence. MNCs mainly formulated their drugs in India, importing the bulk drugs from their home countries; their contention being that the locally available bulk drugs were not of the desired quality. In the process, not only were technological externalities and knowledge transfer absolutely minimal but Indian drug prices were among the highest in the world (Ramani and Venkataramani, 2001; Greene, 2007). Thereafter, the evolution of the Indian pharmaceutical industry can be divided into four phases.

2.1. First attempts to reduce dominance of foreign firms

In order to reduce the dependence on imports and Western MNCs, at least for vitally needed antibiotics, the government of India undertook large investments to establish public sector enterprises (Singh, 1985). The most important among these were 'Hindustan Antibiotics Limited' (in 1954) and 'Indian Drugs and Pharmaceuticals Limited' (in 1961). The move was useful and timely, but it was not a comprehensive response to the country's healthcare needs.

Inspired by the economic growth models of Russia and China, throughout the 1960s and 1970s, India, like most other developing countries, adopted inward looking trade and investment policies. The objective was to minimize dependence on imports and develop an industrial base to serve the needs of its citizens, while promoting market competition and curbing monopolistic and oligopolistic tendencies. The ensuing 'import substitution' policy took the form of a complex system of price controls, high import duties and export subsidies[4]. In addition, under the guise of controlling profiteering by the private sector, the Indian government practiced the 'License Raj' i.e. 'rule by license' by which any firm wanting to expand its manufacturing base, export or import, had to get a license from the government to proceed.

The system of price controls was particularly stringent on pharmaceuticals as compared to other sectors, in the interests of social welfare. In the wake of the Sino-Indian war in 1962, in order to ensure accessibility of drugs to serve wartime needs, the 'Drug display of Prices Order' (DPO) and the 'Drug Price and Control Order' (DPCO) were passed under the 'Defence of India Act' in 1962 and 1963 respectively. Over time, these two acts were merged into one and price control was introduced in 1970 for a long list of 'notified' drugs that were deemed essential (Kaushal, 2007). The objective was to curb profit margins and promote access to drugs.

[3] Some parts of this section draws upon previous articles by the author: Athreye et al. (2008), Ramani and Maria (2005), Ramani (2002), Ramani and Venkataramani (2001).
[4] See Burton (1998) for a survey of import substitution policies adopted by India and other developing countries.

This system of regulation was continually opposed by both MNCs and fledgling Indian companies in the pharmaceutical sector. They argued that while high import duties were responsible for pushing up domestic prices, price ceilings were discouraging the flow of investment into the industry by depressing the earnings of companies. Besides, the 'License Raj' promoted public corruption and diverted the efforts of firms towards securing fiscal and tariff concessions, permits and licenses, from the government rather than seeking support for R&D in any form.

Against this backdrop, India still adhered to a very tight system of IPR. At the time of independence in 1947, India's IPR system was defined by the 'Indian Patents and Designs Act of 1911', which itself was based on the British 'Patent Act of 1852'. Under this regime, patent holders were allowed exclusive rights to make, sell and use both new processes and products for 14 years from the date of filing in India. Re-engineering of branded drugs was not allowed and almost all patents of branded drugs were held by MNCs.

Thus, after twenty years of the 'License Raj' and an import substitution policy, 80% of the market share was still held by foreign controlled firms in 1970. Indian firms had capabilities only in formulations. Prices of drugs remained among the highest in the world, partially due to import duties, but mostly because firms were focused on brand competition and promotional activities (Lall, 1974a, 1974b). Indian consumers suffered from a shortage of essential drugs and a crisis in terms of healthcare provision. MNCs on the other hand fared well: they were in India "not only the most profitable among manufacturing firms in the country generally but also among all types of foreign controlled enterprises, including those in non-manufacturing sectors" (Lall, 1974b; p.163).

2.2. Development of re-engineering capabilities and conquest of internal markets

There were two possible solutions to the healthcare emergency at the beginning of the 1970s. Either medicine could be imported in large quantities as essential commodities or incentives could be provided for the development of the local pharmaceutical industry. The Indian government opted for the latter solution.

By the mid 1950s itself, it had been brought to the attention of the Indian Government that most of the developed countries had put in place a strong IPR system with full product and process patents only after having acquired a certain level of technological competence in knowledge-intensive sectors and a good competitive position in the international market in targetted fields. Accordingly, in 1957, the Indian government appointed Justice Ayyangar to investigate this matter, and his report submitted in 1959, recommended that only process patents be recognized for essential commodities like food and drugs. But, it was after a little more than a decade that his recommendation saw the light of day in the form of the new 'Patent Act of 1970', which came into force in 1972. It is to be noted that even in 1972, developed countries like Sweden, Switzerland, Spain, Italy and Japan did not allow for product patents in pharmaceuticals, thus revealing the retard of the Indian government in opting for this much practiced option of industrial development in other parts of the world.

The Indian Patent Act of 1970 essentially constituted a 'narrowing' of the IPR regime with provisions for commercializing independently developed copies of branded drugs, if the production process was significantly different from that used to manufacture the branded product. Thereby, the incentives for Indian firms to become second innovators were increased. At the time, neither MNCs nor scholars expected the industrial organization to change much; it was essentially viewed as a possibility for the public sector to accumulate technological capabilities and serve the low-income communities directly (Lall, 1974b, Redwood, 1994).

However, Indian firms correctly sized-up the 'window of opportunity' opened by the new process patent regime. Leading Indian pharmaceutical firms began to invest in building re-engineering capabilities and started producing essential drugs – slashing market prices heavily. Indian firms even entered into production contracts with the original MNC inventors, permitting them also to enjoy lower costs, and a greater mark-up. As a result, slowly but surely, the market shares changed, bearing witness to the downfall of the previous market leaders, namely MNCs.

In 1970, eight of the top ten firms in the Indian market were MNCs, but by 1995, only four of the top ten firms were MNCs (Athreye et al. 2008). The share of MNCs in the Indian market was 68% in 1970, 60% by 1978 and 50% by 1980 (Chaudhuri, 2005). By the mid-1980s leading Indian pharmaceutical firms were producing both bulk drugs and formulations for the domestic market. By the end of the 1980s, India was exporting bulk drugs and final therapeutics, supplying many parts of the developing and developed world at lower prices and edging towards a positive trade balance. But most important of all, with the increase in market supply, the Indian public healthcare system was finally able to stand up on its feet and the proportion of the poor with access to basic drugs increased.

To conclude, the change in the IPR regime coupled with the dynamic response of local firms to acquire capabilities in all stages of drugs production led to a sharp reduction in import dependence and MNC domination. But, this would not have been possible had India not been equipped already with scientific capabilities in the form of public laboratories skilled in creating new processes; and universities producing large numbers of science graduates. The demand side also supported the new trajectory as Indian consumers revealed themselves to be extremely price sensitive.

2.3. Development of regulation handling capabilities and assault on international markets

The 1990s saw a number of extreme changes in the Indian regulatory environment which influenced the accumulation of technological capabilities in almost all sectors, including pharmaceuticals. In 1991, the economy was liberalized and the pharmaceutical sector was de-licensed: it was no longer necessary to get a license from the concerned Ministries to expand the manufacturing base, export or import goods. The price control regime, DPCO, was modified and 50% of the drugs were removed from price control in 1995 and only 76 drugs (26%) remained under price control by 2004 (OPPI, 2004). A new regulatory agency: 'The National

Pharmaceutical Pricing Authority' became functional in 1997 to coordinate the regulation of prices.

Economic liberalization had a remarkable effect on the growth of the pharmaceutical industry, with more firms entering the market, and the established ones increasing their manufacturing base. Production, exports and imports shot up and the industry grew rapidly in the 1990s, with an average annual growth rate of 15% for bulk drugs and 20% for formulations (OPPI, 2001).

Interestingly, the rise of exports was partly due to the foray of Indian firms into regulated markets of Western countries, with the principal target being the USA. During the 1980s, American policy makers had become sensitive to the need for improving access to medicines and curbing the growth of health expenditures in the USA. With this objective, the Hatch-Waxman Act was passed in 1984 to stimulate the market for generics, and as a result, generics manufacturers no longer had to go through a lengthy period of extensive clinical trials. Demonstration of bio-equivalence was sufficient to acquire marketing approval for a generic drug. Ironically, the concerns that prompted the Hatch-Waxman Act were quite similar to those, which had provoked the Indian Patent Act of 1970.

Indian firms with foresight like Ranbaxy recognized that the Hatch-Waxman Act in the USA in combination with the liberal economic policies in India was opening up new 'windows of opportunity'. Such leader firms immediately attracted followers, which also attempted to penetrate the regulated markets of the USA and Europe (Athreye et al. 2008). In addition to exporting medicines to unregulated Southern markets, from 2000 onwards Indian firms began to get supply contracts from international organizations (e.g. WHO, PEPFAR program[5], Global Fund etc.) that were supporting public health programs in developing countries, thus responding effectively to yet another 'windows of opportunity'.

In order to sell generics in these regulated markets, Indian firms had to upgrade their regulation handling capabilities, i.e. initiate routines to document the entire production process under specific formats. To enter a Western market, say that of the USA, Indian firms had to upgrade their 'Drug Master Files' procedure by increasing the comprehensiveness of the details supplied on the manufacturing and distribution process, to satisfy the requirements of the US Food and Drug Administration (FDA). The generics producer also had to prove that its manufacturing methods conformed to current 'good manufacturing practices' (GMP), as defined in the US Code of Federal Regulations. Then it could apply for an ANDA or 'Abbreviated New Drug Application' under four types of filings termed paragraphs, the last even permitting entry of generics before patent expiration. Ranbaxy was the first Indian firm to use the ANDA filing route to enter the US generics market, leading others to follow. It used the steady but low return Paragraph 1 to Paragraph III approach of ANDA fillings, whereby the generic manufacturer entered the market only after expiry of the product patent to secure a niche in the US antibiotics

[5] the US President's Emergency Plan AIDS Relief.

segment[6]. Such building of regulatory handling capabilities resulted in India having the largest number of manufacturing units validated by the FDA outside of the USA by 2007: India had 75, Italy 55, Spain 25 and China 27 (Tribune des droits humains, 2007).

Similarly, after 2000, in order to supply public health programs in developing countries supported by international organizations such as the WHO, Indian firms had to comply with a prequalification process of product-selection and regulations related to WHO-GMP. Thus, though these requirements did not affect the small and medium scale suppliers of intermediate or bulk drugs, the leading pharmaceutical firms that supplied international markets adopted GMP, even when it was not required within India. The WHO also demanded other complementary practices such as submission of 'Drug Master Files' giving details of the firm and its system for ensuring quality, documentation, validation, self inspection and internal audit. The success of the Indian firms in acquiring regulation handling capabilities is illustrated in the fact that on antiretrovirals, out of the 85 products selected by the WHO to treat the HIV/AIDS epidemics in the developing world, Indian firms such as Ranbaxy, Cipla, Aurobindo or Matrix Laboratories prequalified for the supply of 60 products in 2009[7].

2.4. The quest to build new drug discovery capabilities in the post-TRIPS era

Hot on the heels of liberalization, India became a member of the WTO in 1995 and thereby changed its regulatory framework to comply with TRIPS. Between 1994, when TRIPS was ratified, and 2005, when it came into effect, three amendments to the patent law of 1970 were passed in the Indian Parliament in 1999, 2002 and 2005 successively to make it TRIPS compliant. On the one hand, the rising prowess of the Indian pharmaceutical sector was noted: India ranked 13th in terms of value and 4th in terms of volume of pharmaceuticals produced in the world by 2005 (Gehl-Sampath, 2008). On the other hand, the Indian pharmaceutical market being extremely competitive with very low margins over cost, the elimination of innovation through re-engineering initially seemed daunting and many scholars predicted a gloomy future.

For the moment, shifting to a TRIPS compliant regime does not seem to have hurt the industry. Indeed, the Indian industry is adapting in a number of ways, and probably would have gone in these directions anyway even in the absence of TRIPS. In particular, Indian firms are noted to exercise three types of strategic responses to TRIPS. First and foremost, R&D is targeted towards the copy of drugs, vaccines and diagnostics that are off-patent or are soon to be off patent, especially in regulated Western markets. Second, Indian firms are vying to participate

[6] On the other hand, Dr. Reddy's Laboratories adopted the aggressive strategy of Paragraph IV filings, which involves invalidating existing patents or producing non-infringing process through a costly process of litigation; a high-risk strategy due to the litigation costs involved and the 180-day market exclusivity that the firm wins on a successful challenge. Though Dr. Reddy's Laboratories got six-month exclusivity for selling Fluoxentine 40mg capsules in US, it also received a severe set back when it lost the AmVaz case to Pfizer. Thus, the two early entrants differed quite markedly in their propensity to take risks. Other Indian firms then began to follow the example set by Ranbaxy and Dr. Reddy's Laboratories, but the low-risk strategy of Paragraph 1-3 applications is the more commonly followed model. Such entry into Western regulated markets meant that the Indian pharmaceutical firms also had to set up litigation teams and invest in paying for the corresponding dispute settlement procedures.

[7] For more information, see http://apps.who.int/prequal/, last visited in September 2009.

in the international division of labor for the creation of new drugs by Western MNCs by offering contract research and custom manufacturing services, bioinformatics services for genomics based drug research, and carrying out clinical trials. Indian companies realize that they cannot match the deep pockets of Western MNCs as far as R&D budgets are concerned but want to avoid exclusion. By providing contract services to Western MNCs in the latter's new drug discovery endeavors, they hope to build new dynamic capabilities either in the pre-competitive upstream research stage or in downstream clinical trials stage (Ramani and Maria, 2005). Third, and in a smaller measure, Indian firms are initiating strategic alliances (more in US) and outright acquisitions (more in Europe) for a variety of objectives ranging from access to technology assets, market penetration and a better understanding of local regulation (Greene, 2007).

Indian firms at present are still facing the heavy challenge of catching-up in terms of developing drug discovery capabilities. While pursuing this course, two new kinds of threats from MNCs are rearing their heads.

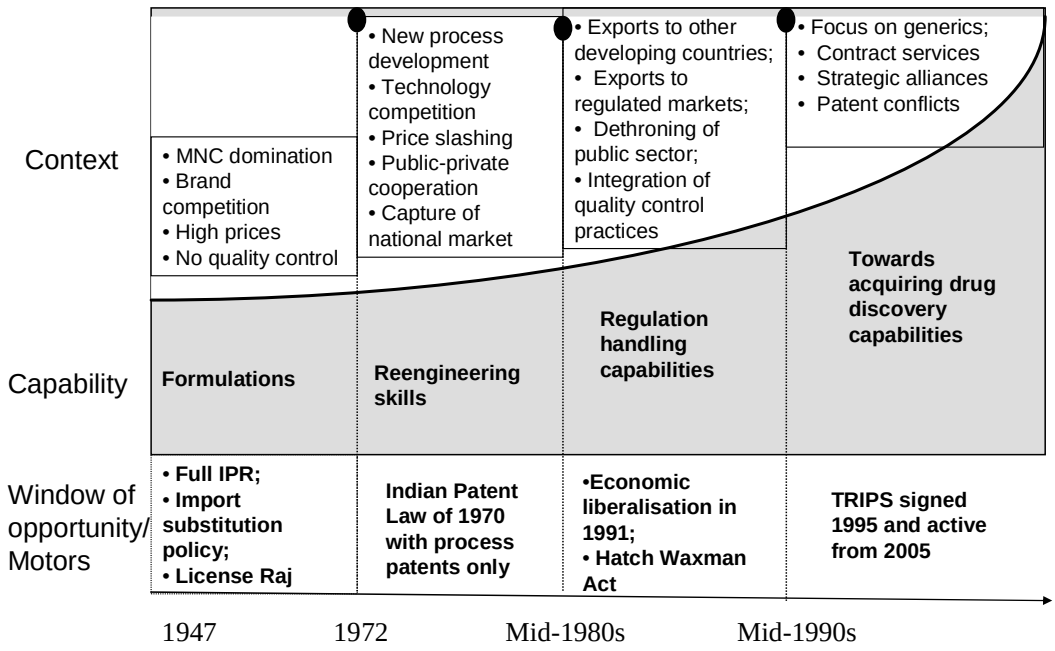
First, Indian firms have become so capable that they are becoming attractive to global players. For instance, the Indian industry has been very marked by the buying-out of its star performer Ranbaxy, by the Japanese company Daiichi-Sankyo making the threat of foreign buy-outs a credible one for all major Indian firms. Daiichi-Sankyo has business operations in 21 countries, while Ranbaxy is present in 56 countries, including Emerging and Transition economies in which Daiichi has not entered. Ranbaxy is among the international leaders in generics with a renowned low-cost manufacturing infrastructure, but it is struggling to gain expertise in biotechnology and new drug development. Daiichi is weak in generics, but has a good R&D expertise and a solid position in patented drugs. A cash infusion of about $1 billion brokered under the deal will presumably enable Ranbaxy to retire debt and increase growth. The growth potential for generics, especially in Japan, is high. These complementarities led the founding family of Ranbaxy to accept the offer of Daiichi-Sankyo to buy out their 34.8% stake and make open offers as per Indian regulations for an additional 20% of Ranbaxy's share in June 2008, with the assurance that Ranbaxy will operate as an independent subsidiary of Daiichi under the leadership of its current CEO Malvinder Singh. The acquisition of Ranbaxy, a jewel in India's pharmaceutical crown, by the Japanese firm, struck an emotional blow to the Indian public, even as the business pundits pointed out the rationality of the merger. It is not unlikely that other such acquisitions will occur in the future (Singh, 2008; Basheer, 2008). Thus, the threat of some more leading Indian pharmaceutical firms losing their 'Indian citizenship' is a challenge to be reckoned with.

Second, under the stronger IPR regime ushered in by TRIPS, there is a growing concern about the conflict between pursuit of monopoly profit and satisfaction of public interest in terms of access to life saving drugs. In India, there are an increasing number of patent disputes regarding life saving drugs between patent owners, generic producers and the public. There are inherent tensions at the moment in courts between MNCs, which want to protect their branded drugs, and civic associations and NGOs, which demand better access to drugs for the poor through the production of generics. The MNCs call for legal clarity on what can be patented, what can be considered ever-greening of patents and what kind of patents can be by-passed in the interests of the public. For instance, using a pre-grant opposition mechanism introduced in 2005 in the patent law, Indian firms and a civic association challenged Novartis' application for a patent on its

anticancer drug Glivec. The patent was rejected on the ground that the API was based on a derivative of a molecule known before 1995, which "does not result in the enhancement of the known efficacy of the substance" as stated the Section 3(d) of the Indian Patent Act (Srinivasan, 2007). Furthermore, these problems are exacerbated by a lack of coordination between governmental bodies. For example, Cipla gained marketing approval for a generic version of a lung cancer drug from the Central Drugs Standard Control Organization (CDSCO), which operates under the aegis of the Ministry of health and family welfare, while the original innovator Roche was granted a patent by the Indian patent office at the same time for its branded drug Tarseva (Gehl-Sampath, 2008). Again, in the interests of the public, the Indian court sided with the generic producer. Only the future will tell how the interests of the public will continue to be upheld under the TRIPS regime given the pressure from the MNC pharmaceutical lobbies. In turn, such cases are also often cited by MNCs to justify their lack of enthusiasm to introduce new products in India.

Thus, the future of the Indian industry will depend on how the triple challenge, namely of catching up in terms of new discovery capabilities, surviving in a global market and being socially responsible in a poverty stricken country, is played out. The evolutionary trajectory of the Indian pharmaceutical sector as presented in this section is summarized in figure 1. To sum it up, by identifying and catering to several 'windows of opportunity' opened by regulatory shifts in India and abroad, Indian pharmaceutical firms have successfully lowered the domination of MNCs in the domestic market, and built manufacturing capabilities, integrating backwards from the formulation stage to the production of APIs.

Figure 1: Evolution of the Indian Pharmaceutical sector



3. Brazil

Brazil had a head start over India in industrialization, thanks to attaining independence from colonial rule in 1822, more than a century earlier than India. By the beginning of the 20th century, it had a nascent pharmaceutical industry and some public laboratories. Yet, today, unlike India, Brazil suffers from two major handicaps with respect to the pharmaceutical sector: market domination by foreign multinationals and a lack of backward integration of local firms to incorporate manufacturing capabilities in API. Both these limitations are likely to worsen in the future given the increasing presence of new players from emerging countries headed by India and China. Why? This is the question we seek to answer in this section.

3.1. No industrial policy during critical technical shift

By the end of the 19th century, as in Europe and USA, a handful of Brazilian firms were involved in the production of mineral-based medicines on a small scale. In addition, due to the suffering inflicted by the spread of epidemics among the urban population, Brazil established a set of public laboratories between 1892 and 1927 such as the: 'Bacteriological Institute', the 'Butanta institute', 'Oswaldo Fiocruz' Institute and the 'Biologic Institute', with the mission of developing and producing serums and vaccines. Thus, by the 1930s the Brazilian pharmaceutical market consisted of: (i) public institutions devoted to the development and production of vaccines and serums to abate epidemics of plague, smallpox and yellow fever and to treat snakebites; (ii) national firms involved in the production of medicines; and (iii) foreign firms also committed to the production of medicines. The last group accounted for only 13.6% of the pharmaceutical market at this time (Queiroz, 1994).

This situation changed dramatically with the ushering of the antibiotics revolution triggered by the spectacular success of penicillin during WWII. Leading Western pharmaceutical firms began to explore the possibilities of creating other antibiotics and drugs based on biological survey, assays and chemical synthesis. They developed technological capabilities in chemical synthesis and commercialized an array of drugs for a variety of infections that were superior to any produced by a developing country firm, including the existing Brazilian ones. The Western firms expanded their scale of production and continued to reap economies of scale as market demand in their nations got a boost with the introduction of systems of universal insurance (both public and private) and State health security schemes. Then they began a serious offensive of internationalization with augmentation of manufacturing capacity worldwide.

This expansionist trend of MNCs conflicted with the aspirations of Brazilian firms, which were striving to promote industrialization and self-sufficiency through adopting the 'import substitution model of industrialization'. In this perspective, the patent system was overhauled in Brazil in 1945 to permit only process patents and encourage reengineering. However, these positive incentives were nullified in the 1950s by a macroeconomic policy that attempted to attract foreign direct investment (FDI) through deferentially low exchange rates. As a result of particularly low exchange rates in the pharmaceutical sector, Western MNCs found it in their interest to import raw materials and equipment from their home countries on a large scale and

expand their operating base in Brazil. On the other hand, the measures taken to facilitate the import of equipment could not be exploited by local firms because the scale of imports of equipment that was needed to be competitive with MNCs was beyond what any Brazilian firm could afford.

As a consequence of the absence of an industrial policy to protect national industries and the overwhelming presence of foreign firms armed with superior drug-manufacturing technologies, Brazilian firms were caught in a lurch and ceded their place to foreign firms. Frenkel (1978, quoted by Urias and Furtado, 2009)[8] notes that the policy to attract foreign capital inflow combined with the competitive advantages of large firms from the USA and Europe brought about a denationalization of the pharmaceutical sector through the exit of local firms and buy-outs by MNCs. Between 1958 and 1972, 43 domestic companies were acquired by foreign firms, mostly American (Bermudez, 1992, quoted by Urias and Furtado, 2009).

This change in market composition was the beginning of a long period of steadily rising domination by foreign MNCs, which furthermore did not involve themselves in R&D activities or local production of raw materials. By the 1950s, the country had about 500 pharmaceutical companies, of which very few were Brazilian, while the market shares of the foreign firms rose to about 47.1%. This figure increased drastically to 73.3% by 1960, with only 4 national firms being among the top twenty (Queiroz, 1993).

Such trends were perceived to be leading to a real problem in terms of access to medicines with prices being too high and some essential drugs not being available in large enough quantities. Therefore, the State moved in to intervene in the pharmaceutical sector in several ways to remedy this situation:

- A system of price controls was put into place in 1968. An Inter-Ministry Council for prices was charged to limit price hikes and ensure that the price increases in medicines were in general lower than the inflation rate (Romano and Bernardo, 2001, quoted by Urias and Furtado, 2009).

- Even process patents were removed in 1969 to provide further incentives for the development of re-engineering capabilities and the production of a greater variety of drugs (Frischtak, 1989, Queiroz, 1993, Robine, 2008, Urias and Furtado, 2009).

- A public procurement agency, the CEME (Central de Medicamentos) was created in 1971. At first, its mission was to purchase and distribute medicines in hospitals. Two years later, the CEME was also charged to diversify the public provision of medicines and in the process support the development of a '100% Brazilian' pharmaceutical industry. It was instructed to practice this policy right from the purchases of raw materials to final products, encouraging national initiatives and technology transfers (Queiroz, 1993).

[8] All references that are quoted by Urias and Furtado (2009) are in Portuguese, a language that is not known to either of the authors of this paper. Hence, these articles are not cited in the references.

Still by the beginning of the 1980s, a veritably autonomous local industry, capable of producing its own API and finished products was nowhere in sight. Foreign MNCs continued to dominate catering to about 82.7% of the Brazilian market (Queiroz, 1994). Visibly, even the total absence of patent protection coupled with the operations of public agencies like the CEME had not been sufficient to stimulate local production. Why?

A singular lack of consistency in the implementation of industrial policy thwarted the entire process. For instance, the CEME passed under the aegis of different organisms over time, with each having a distinct immediate target. In 1971, the CEME operated under the 'Ministry of Health' but in 1974 it was moved to the 'Ministry of Planning and Social Welfare'. According to Queiroz (1994), this shifting status resulted in a reduction of CEME's powers to act effectively as a public procurement agency and intervene in the market.

Indeed, from the 1960s to the 1980s, there was a constant confrontation between the advocates of two types of logic (Andréa-Loyola, 2009). One pushed for an 'autonomous' route to development, which favored the building of a national pharmaceutical industry committed to the production of raw materials, as well as finished products, to increase self-sufficiency. The other argued that satisfying local demand, whether through the production of local firms or the production of foreign MNCs was primordial. This more 'neo-liberal' or 'dependant' logic was largely supported by MNCs (via the lobbying of ABIFARMA, the Brazilian pharmaceutical association made of MNCs). Thus, the turbulent operations of the CEME basically revealed the competition of these two groups. More generally speaking, the 'come and go' policy exercised during the 1970s and the early 1980s by which the structure and ordering of public agencies shifted according to the whims of the government also reflected the struggle between the two lobbies.

3.2. Lagging industrial policy in a turbulent macroeconomic context

During the 1980s, industrial policy on the whole was largely constrained by the vicissitudes of macroeconomic policy (Suzigan and Furtado, 2006). The Brazilian economy entered into a grave economic crisis due to serious external debt. Being feebly competitive in many sectors, Brazil tried to improve its balance of payment through reduction of public investment and institutional changes. As a result, even while Brazil made great progress in terms of expansion of manufacturing capabilities in the pharmaceutical sector, such progress hid a strong dependence on imports in some niches. In the end, the problem of lack of backward integration over the different operations of production was never solved, but simply displaced.

For instance, budget cuts were imposed on nodal bodies such as the 'National Scientific and Technical Development Fund' and the discretionary powers of the 'Economic Development Council' in the decision making process was steadily lowered[9]. Moreover, public investments in education and infrastructures were also slashed. Brutal stopping of plans for scientific and technological development as well as programs for sectoral development led to a serious skills

[9] The former was responsible for the financing of scientific and technological projects, while the latter had been charged with the mission of defining the targets for economic development.

constraint in terms of qualified scientists, technicians and engineers. These serious drawbacks undermined the 'social capabilities' of Brazil and also acted as a brake on industrial development during the so-called 'lost decade'.

To top it all, the government initiated protectionist measures to reduce imports and lighten the external debt. These had maximum impact on the pharmaceutical industry. The government established a system of 'market reservations' for products that could be locally manufactured, fixing high tariffs or banning imports, and preventing the duplication of industrial projects by limiting market competition in favor of domestic firms (Queiroz, 1994, Urias and Furtado, 2009, Robine, 2008).

Finally, while waiting with anticipation for the pharmaceutical industry to contribute to an improvement of the trade balance, the Brazilian government launched a back-up plan. The public sector moved forward to attempt to develop technological capabilities needed to produce important API in collaboration with the private sector. In 1984, the CEME launched a collaboration with the CODETEC[10] and some private pharmaceutical firms. The objective of this project was to identify research output from universities with commercial potential and explore ways in which they could be brought to the market[11]. CODETEC agreed to develop a set of targeted technologies related to the API. In return, the CEME assured purchases of the same and the associated firms could manufacture and sell the concerned products on the final market. With an investment of $5 million till 1990, the know-how to produce about 60 API was developed, but among these only 13 reached the production phase. Even after the production process had been developed at a pilot scale on public funds, the rest of the targeted API were never produced by the small firms associated with CODETEC (Queiroz, 1994).

Thus, the policy measures, which were expected to draw the local industry into the catch-up process in terms of production of API and finished products in the short run, and to provide incentives for augmentation of innovation capabilities in the medium term, were only partially successful. Indeed, against all odds, the mix of State macroeconomic and industrial policies during the 1980s only contributed to widen the fundamental fragility of the Brazilian pharmaceutical industry.

For instance, while the weak degree of backward integration was still flagrant and foreign firms still held more than 80% of the market, there was mixed success in reducing imports dependence. Imports of medicines stayed on average at $15 million between 1981 and 1989, i.e. less than 1% of the local production, and imports of API decreased from $310.7 to $278.3 million between 1981 and 1987 (Queiroz, 1994, Urias and Furtado, 2009). Furthermore, domestic production of API steadily increased from $268 to $521 million between 1982 and 1987. However, imports of intermediary products requiring one or two processes to be converted into API increased significantly. Thus, the fall in the imports of API hid and was largely matched

[10] The CODETEC (Company for technology development) was created in 1976 through collaboration between the State University of Campinas (UNICAMP), the Ministry of industry and trade, and a group of firms, mostly from the public sector.

[11] In 1994, CODETEC had its own installations in the campus of the 'High Technology of Campinas (3500m2, 12 laboratories and some pilot plants specifically for the development of processes of fine chemicals). Out of 100 employees, 60 were researchers (Queiroz, 1994).

by an increase in the imports of intermediate products (required for the production of API) from $37.4 to $115.5 million, though on the whole there was an improvement in the trade deficit[12].

Public-private cooperation, though well intentioned was a failure due to institutional constraints and ineffective responses of firms. At the outset, any API production was subject to regulation on the margin over costs. Keeping this in mind, the consortium targeted API astutely as a function of their (low) cost of development and their (high) potential demand. The last few stages of the production process of API were not capital intensive and therefore compatible with low profit margins. But there were other intermediate steps which required high fixed cost to enjoy returns to scale and such fixed costs could not be borne given the regulation on profit margins. Therefore, more often than not, the local firms renounced the production of API and instead concentrated on the production of finished products, for which MNCs' imports were highly taxed or banned. Moreover, the production of such finished products was enabled by large imports of raw materials for which tariffs were still low given the absence of local production.

To top it all, the most unexpected outcome of the gamut of regulatory changes was the responses of the Brazilian firms. Even though all technologies could be freely imitated, there was no large scale investment in the acquisition of re-engineering skills. Being severely constrained by a lack of funds, local firms could not invest in costly equipment to expand their manufacturing base. Consequently, under a 'market reservation' system, instead of giving competition to Western MNCs, Brazilian firms began to imitate them. Local firms imported raw materials to manufacture finished products just like the MNCs and then competed in the final market by focusing on the quality and quantity of their medical sales force. A 'commercial logic' was adopted, partially imitating the behavior of MNCs. The commercial logic followed by MNCs was based on the premise that the development and commercialization of new medicines had to be ensured by a high investment in marketing and advertisement. In contrast, the commercial logic followed by Brazilian firms was founded solely on the dedication of large resources to exploring the best strategies for product differentiation with competing brands (Frenkel, 2001, quoted by Urias and Furtado, 2009). Against the backdrop of high inflation rates, besides marketing outlays, Brazilian firms invested their modest resources in treasury bills, offering high rates of interest, rather than R&D.

3.3. Time for critical regulatory shifts with mitigated effects

The 1990s witnessed three types of radical regulatory changes in Brazil: (i) liberalization; (ii) a reinforcement of IPR; (iii) a new drug policy and public procurement. Going beyond sectoral specificities, these institutional shifts offered little room for the consideration of local industry,

[12] Besides, this increase in the imports of API and intermediate products can be explained by the activity of MNCs present on Brazilian territory. In the face of constraining national fiscal policy, MNCs were often tempted to opt for advantageous transfer prices, i.e. to repatriate a part of the profits realized by billing at unduly high prices the intermediate products and API supplied to their Brazilian subsidiaries. In addition, the period was market by high inflation rates and several devaluations of the real currency, which generated a dramatic increase in the value of imports.

and thus failed to trigger a large-scale rectification of the structural defects of the Brazilian pharmaceutical industry.

Burdened with excessive debt, Brazil was obliged to borrow and adopt a set of economic liberalization policies as decreed by the IMF, including the opening and the deregulation of markets. For instance, import restrictions were decreased, lowering the tariff on pharmaceutical products from 70% to 14% (Sweet, 2007). At the industry level, this had the serious consequence of forcing the exit of local firms on a large scale and induced a second wave of denationalization. The Brazilian economy, already marked by a strong dependence on foreign markets, was made even more vulnerable by the closure of about 1700 production units of intermediary goods destined for the pharmaceutical industry in the first half of the 1990s (Orsi et al., 2003).

Under pressure from the US Trade representatives, from 1991 onwards, there was a collective reflection on how to reinforce the IPR regime to attract FDI. In 1996, without even making use of the transitional period permitting a developing country to implement TRIPS by 2005, Brazil proceeded with a new reinforcement of its patent regime to comply with TRIPS[13]. By a Presidential decree both product and process patents were reintroduced with a 20 year validity period. Moreover, a pipeline protection was implemented ensuring patent protection for medicines developed prior to 1997 under the condition that these medicines were already patented in another country and had not been marketed previously in Brazil. Accordingly, instead of following the minimum standards required by TRIPS to provide patent protection to medicines after 1995, the Brazilian Law introduced a legal possibility for firms to gain patent protection and exclusive marketing rights for medicines before this date, forcing firms manufacturing copies of the same to stop production.

Starting from 1991, the drug policy was progressively changed. First, the 1980s price control scheme was dismantled and price ceilings on many of the drugs were removed. As a consequence, firms were inclined to raise their prices so that they could reconstitute their profit, which had been seriously affected by the crisis of the previous decade.

In turn, against the backdrop of repeated devaluation of currency and soaring inflation and hyperinflation, access to medicines was made even worse. In this context, to induce competition and improve access to essential drugs, a formal system of public bidding via the so-called ‘Law of Tenders’ was put in place in 1993. This procedure channeled public procurements representing 26% of domestic market sales through ‘open auctions’ (Sweet, 2007). Only price was taken into account without much attention being paid to quality, leading to very stiff price competition in the market. Four years later, the mandate of public procurement program was further refined by the ‘basic pharmacy program’, which was set up with the specific objective of improving access to 40 essential drugs in compliance with the ‘right to health’ instituted in 1988 in the Brazilian Constitution.

The last pillar of the new drug policy consisted of the promulgation of the ‘Generics Act of 1999’ following the recommendation of an experts group. On the supply side, the objective was

[13] During the Uruguay Round and even before the ratification of TRIPS in 1994 by the countries members of World Trade Organization, Brazil was the target of pressure and commercial sanctions from the United States from the end of the 1980s.

to improve the quality of drugs sold and to fuel market competition. On the demand side, the purpose was to increase the consumption of generics (cheaper than branded drugs), with the help of public authorities investing massively in campaigns to inform people about the quality of generics. In the same year, ANVISA, the counterpart of US Food and Drug Administration, was created to monitor the security, efficiency and quality of drugs marketed in the country[14]. Furthermore, the law insisted that generics be at least 33% cheaper than branded drugs. Finally, the promotion of the national industry was taken into account. The government's implicit argument was that though the fixed costs of production would increase due to the implementation of higher standards with respect to quality of drugs, local firms which complied could enter a larger generics market. Predictably, the 'Generics Act' provoked strong reactions from MNCs, which saw in it a move designed to challenge their local market shares[15].

In practice, the 'Generics Act' regulates the promotion, packaging and marketing of generics in Brazil. It must be noted that until then, as in other developing countries, Brazil authorized the production and marketing of copies of branded drugs or 'similars'. These medicines contained the same API, displayed the same therapeutic indications, the same strength or the same mode of administration as the branded drug patented abroad. However, local producers did not have to demonstrate the equivalence of their products with the branded drugs through the provision of bioequivalence data. Now, the 'Generic Act' raised the standards by requiring firms wanting to launch new copies to get marketing approval through completing bioequivalence studies. Only in this manner, the generic could be deemed equivalent to the branded drug (Sweet, 2007). Thus, three types of drug are currently available on the Brazilian market: branded drugs, generics and similars. But, only similars which were launched before 1999 can be in the market till 2014, being permanently banned thereafter.

Definitely, Brazilian firms recognized the 'Generics Act' as a 'window of opportunity' to develop technological capabilities. The Generics Act is inducing Brazilian firms to move towards a 'technology based competition logic' (Frenkel, 2001, quoted by Urias and Furtado, 2009), under which they are modernizing their production units and developing innovation capabilities. For instance, between 2000 and 2003, generic producers in Brazil invested nearly a billion dollars in the construction and modernization of units (Bermudez and Oliveira, 2004). About 1140 new pharmaceutical products were granted marketing approval between 2000 and 2005. The generics market itself increased from 1% of total pharmaceutical market in terms of both value and volume in 2000, to 10.7% in terms of value and 13.5% in terms of volume by 2006. The increase in market size has clearly benefited the Brazilian firms as the number of local firms among the top 20 generics producers in Brazil increased to 7 holding about 25% of the market share by 2005[16].

To conclude, where does Brazil stand today in terms of catching-up in the pharmaceutical sector?

[14] The mission of ANVISA also covers price control and counseling of the 'National Agency' in charge of granting patents, regarding the assessment of drug novelty.
[15] With campaigns proclaiming the quality of the original API, while hinting that the quality of generics could be mediocre.
[16] See www.progenericos.org.br, last visited February 2010.

Brazil ranks today among the top ten largest pharmaceutical markets of the world with retail sales in 2006 of $8.1 billion, but 70% of the market is still held by foreign firms (Cohen, 2000). However, there has been a marked evolution in the composition of foreign firms dominating the market. In the last century, foreign firms referred uniquely to Western MNCs. Today, this group has been joined by Chinese and Indian pharmaceutical firms. For instance, eleven Indian firms have established local affiliates with some manufacturing capacities (Sweet, 2007). Indian firms hold 10.3% of the Brazilian generics market today and intend to continue their offensive to increase their market shares.

Dependence on foreign imports continues. The industry continues to import more than 90% of its raw material and in 2007 Brazil recorded the huge deficit of $2.7 billion, more than double of the value in 1997 (Urias and Furtado, 2009). Its dependence on imports is not due to lack of technological competencies, but due to the fact that the initial and intermediate stages of the production of API requires a huge capital investment which cannot be amortized given the final market prices and the dynamics of the market[17]. Therefore, instead of investing the manufacturing capabilities in all segments of the drug production process, it makes financial sense to import whatever is necessary.

On the positive side, since 2000, there has been a real effort to renew sector-specific industrial policy and facilitate capacity building. To promote spin-offs and technology transfer from universities, a Brazilian version of the US Bayh-Dole Act of 1980 has been enacted. In addition, other measures have been put in place such as tax breaks for R&D investment, subvention for purchases of machines, funding of public-private joint research projects and to a small measure funding of corporate research projects. Yet, there are discrepancies. For instance, 'Tenders Law' and the 'Generics Act' aimed at improving competition in the pharmaceutical market and accessibility of drugs do not work necessarily for national firms. In particular, the buying of generics to fund the public health programs at the cheapest prices favors new actors (firms from emerging countries) and imports. Indeed Brazilian firms feel discriminated because they have to comply with GMP edicts which do not apply to imports (Hasenclever and Paranhos, 2008).

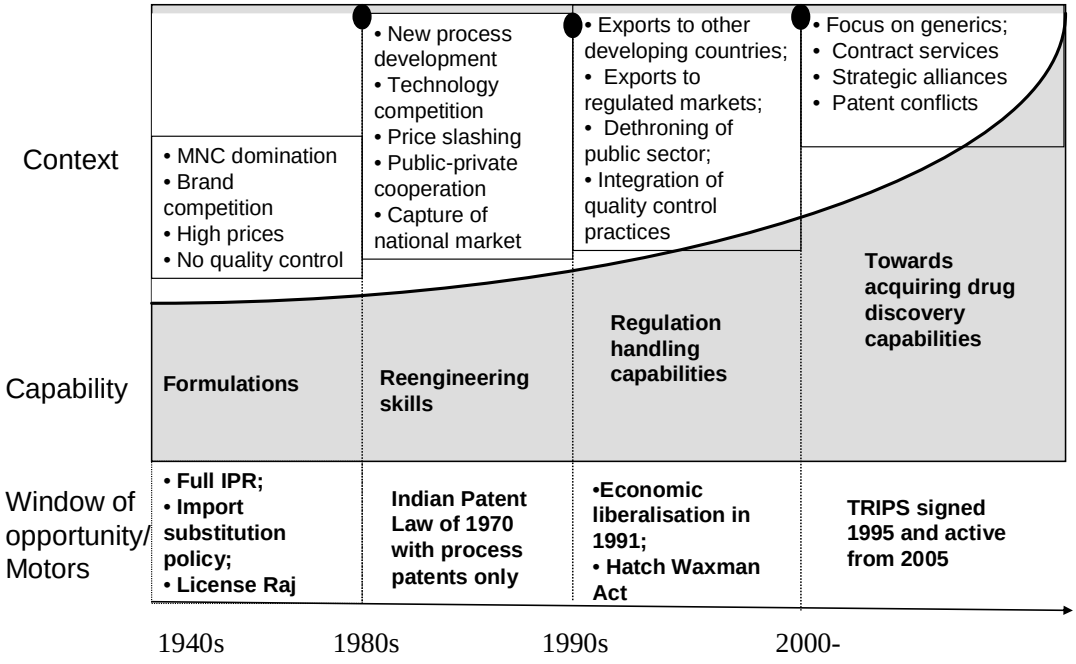
The public sector and public-private cooperation still reigns strong. Far-Manguinhos, a public research institute in pharmaceuticals, is the nodal organization around which a strong and dense network of public institutions and private firms has been constructed. The private firms and public laboratories in this network are involved in R&D programs, aimed at reverse-engineering and copying existing molecules. For instance, Nortec (a spin-off of Far-Manguinhos) is involved in a long-term agreement with Far-Manguinhos whereby it produces the API that Far-Manguinhos uses for the formulation of antiretrovirals (Cassier and Correa, 2008). Further downstream, the State provides steady demand for these drugs. As a result, the public sector today is a provider of serums, vaccines and medicines and also intends to become a provider of diagnostic kits, which is emerging as another social need.

The evolution of the Brazilian pharmaceutical sector is illustrated in figure 2. As it reveals the future of Brazilian firms will depend on the extent to which government policy and public-private cooperation are able to face the challenges posed by the strong presence of foreign

[17] Interviews with C. D'Almeida and B. Fialho – who have extensive work experience in the Brazilian public sector in pharmaceuticals.

(European and Asian) MNCs and the lack of backward integration over all phases of drugs production.

Figure 2: Evolution of the Brazilian Pharmaceutical sector



4. Discussion of Results

Why did two countries such as India and Brazil, starting with a similar resource base and policy rationale exhibit such different trajectories of accumulation of industrial capabilities over time? To answer this question, we start by identifying the pillars of State policy and their rationale. Then we examine the responses they provoked within the industry. We show that the endogenous responses consisted of two parts. On the one hand, most of the time, the predicted and desired outcome was partially realized and on the other hand, there were invariably, other unpredicted responses that emerged. The latter unexpected elements, which were specific to the two countries, pushed them along distinctive trajectories.

4.1. Similar priors but different outcomes

The starting objective of the governments of India and Brazil was to achieve self-sufficiency and autonomy in the pharmaceutical sector. Towards this end, they began by constructing scientific capabilities through investment in higher education. One of the first tasks of the Government of India after independence was to create institutes of higher education and research[18]. In Brazil also, the State invested in higher education with the creation of a network of universities and public laboratories[19].

Then, to translate scientific capabilities into re-engineering capabilities, a lax system of IPR permitting the accumulation of re-engineering capabilities was necessary. Thus, India shifted to a loose IPR regime, allowing for only process patents between 1972 and 2005. Similarly, Brazil had a loose patent system with only process patents from 1945 to 1969 and it did away with the entire patent regime between 1969 and 1997.

Finally, given the large internal size of their domestic markets, for both countries, the policy of import substitution was a reasonable strategy to adopt. Each embraced it to a different degree to curb imports and promote exports and local industries. Thus, in terms of capabilities and public policy, Indian and Brazilian pharmaceutical markets resembled each other by mid-twentieth century. Nevertheless, despite these similarities, the final outcomes after 50 years diverged greatly in terms of the degree of backward integration of local firms, the domination of MNCs in the domestic market and the role of public sector.

A different achievement in backward integration: Both India and Brazil started by creating '*basic manufacturing capabilities*' in formulation by importing bulk drugs and API. At this stage, they acquiring 'packaging skills' or '*skills in formulations'*. Then, they invested in developing '*re-engineering capabilities*' in order to acquire '*production capabilities in bulk drugs and API'*. This enabled further backward integration over the production process and reduced the costs of production, but this was much less in Brazil as compared to India.

In Brazil, more than 90% of the core substances of drugs, the API, are still imported and only a few local firms are involved in their production (Sweet, 2007). In contrast, leading Indian firms have successfully integrated over the different phases of the drug production process, from the formulation of finished products to the more complex production of APIs at competitive prices.

[18] It expanded the network of universities; it set up institutes for technical training such as the Indian Institute of Technology (IIT). It also established research institutions for advanced research outside the university system such as the Indian Council of Medical Research (ICMR), the Indian Council of Agricultural Research (ICAR) and the Council of Scientific, and Industrial Research (CSIR).

[19] Among others, Fiocruz is a public institution in charge of the promotion of public health and social development, through the creation and the diffusion of scientific and technical knowledge. Besides, the National Council for Scientific and Technological Development (CNPq), is a public agency linked to the Ministry of Science and Technology, that works for the promotion of scientific and technological research and for the formation of human resources for research in the country. It works in close relation with the Federal University of Rio de Janeiro and its 'Chemical Institute' founded in 1963 with the support of the BNDE, the Bank for economic development, and the Ministry of Planning.

Traditional and new forms of domination by MNCs: The degree of domination of MNCs seems to be correlated to the degree of backward integration achieved in the two countries, but it is not clear which factor is responsible for the other. It is similar to trying to answer the classic question – which came first, the chicken or the egg?

In Brazil the traditional form of market domination by MNCs still reigns strong. Even the generics supply side contains many foreign firms. A consequence of such dependence is a steady foreign trade deficit in the pharmaceutical sector. The new element in the MNC domination is that new players have joined the big boys – namely Indian and Chinese firms.

In India, the traditional form of domination by Western MNCs was eliminated by the mid 1980s; however, new forms of potential domination are being perceived and giving rise to concern among civic associations, policy makers and Indian firms. At the moment they are taking the form of patent conflicts concerning life saving drugs and the threat of foreign buy-outs. The risks being augured by these trends is not very clear. Will India lose its place as reengineering capital of the world in pharmaceuticals? Will foreign buy-outs again lead to India being a formulation or manufacturing centre? Will market size be reduced on the supply size with delocalization following foreign acquisition?

Internationalization: The evolutionary process in terms of internalization followed a parallel route to the building of manufacturing and innovation capabilities, similarly increasing in complexity. At present, Indian firms are ahead of Brazilian ones not only in terms of technological capabilities but also in R&D, production and marketing capabilities outside of India. They have acquired firms in the USA and Europe and have established production facilities in Latin America and Africa as well. This in turn has led them to also fortify their 'regulation handling capabilities' in order to be a player in the global market.

Different dynamics of the public sector: In India, during the 1960s and 1970s, the public sector was viewed by industry observers as the patron saint of the poor, but in the post-TRIPS era, it is in Brazil that the public sector remains active and vibrant.

In Brazil, from the 1970s and the mid-1990s, though public laboratories were largely committed to the development and transfer of technology to the private sector, success was not evident. However, from the end of the 1990s, the Brazilian State has engaged itself seriously in the promotion public health and this has led to new stock-taking of R&D and manufacturing capabilities[20]. For instance, under the universal access program to HIV/AIDS treatment, Far-Manguinhos ensures the industrial application of technologies developed in both public laboratories and private firms (mostly spin-offs of Far-Manguinhos). By so doing, public sector firms can produce drugs in their own manufacturing units and supply essential drugs to public health programs, which offer a steady demand.

Strangely, in India, after the 1980s, once the basic demands of the public health system were satisfied, the public sector had only a minor impact on the development of innovative

[20] As a result the Brazilian government could bargain price reductions for HIV/AIDS drugs with MNCs advantageously and scale-up the universal access program, which today covers 180 000 people living with HIV/AIDS (Guennif, 2007, De Albuquerque Possas, 2008).

capabilities. Indeed, the role played by some of the CSIR labs (strong in synthetic chemistry), which had been crucial earlier, is deemed insufficient today. At present, the lacuna is in biotechnology and the focus of State policy is on building scientific capacity in targeted niches, promoting public-private cooperation and streamlining regulatory procedures (Chaturvedi, 2007). However, despite such public investment, there have been few start-ups, outside of bioinformatics. Even as suppliers of qualified personnel, universities are found wanting today. Most science graduates have only bookish knowledge and not enough practical knowledge, communication skills or teamwork capacity, requiring firms to invest at least a few years in training the young graduates hired so as to make them productive[21].

4.2. Main reasons for divergent evolutionary trajectories: Different policy design and distinct endogenous responses

As shown in the preceding section, in both India and Brazil, the State was motivated by the same rationale and it implemented similar policies, but the outcomes were very different. Why? First, the impact of policies motivated by the same objective can be different depending on their design, i.e. their content, timing and implementation process. Second, in addition to expected responses, they can also provoke unexpected reactions from stakeholders, as the outcome of a policy cannot be entirely commanded in a market economy. Third, both expected and unexpected outcomes can trigger secondary effects that provoke further change through 'mimicry' and 'bandwagon effects'. It is the distinct features of these three elements: policy design, endogenous response and secondary reactions in India and Brazil that have led to the different evolutionary outcomes. We illustrate this proposition with examples.

Domination by MNCs served by inconsistent policy design? The impact of policy is determined not only by content but also by form of implementation. In both Brazil and India, the rationale of 'import substitution' was a cornerstone of State policy. But, in India, this was followed consistently and comprehensively in the pharmaceutical sector, while in Brazil it vacillated over time. The Indian government did not hesitate between the implementation of an import substitution model and a policy aimed at attracting FDI. Import duties were imposed on all foreign items. In contrast, throughout the period studied, in Brazil there were two lobbies confronting each other. One lobby pushed the 'import substitution' agenda because of the existence of a large domestic market, while the other sought support for opening the market to 'attract FDI'. The MNCs backed up the latter with disastrous effects on local firm strategy.

As a result India seems to have put more of a united front to selectively implement the advice offered by the Washington Consensus. On the other hand, "*compared to India, the much more profound incorporation of the majority of the recommendations of the original Washington Consensus and some of the augmented ones in Brazil have not only been responsible for reducing the efficiency of the coordination of the macroeconomic policies with its National Innovation System, but also explain to a great extent the bad general economic performance*

[21] Comments during interviews with four leading pharma firms in December 2008.

expressed, notably, by slower economic growth" (Nassif, 2007; p.13), during the 'second lost decade' (i.e. 1990-2000).

The above features coupled with the realities of the Indian pharmaceutical market such as razor-thin profit margins and declining prices, made India unprofitable for large scale investment in the view of MNCs. Whereas, the Brazilian market seems to have been simply more comfortable for the Western MNCs, which are now being joined by new players from India and China as well.

Role of perceptions and endogenous responses in catching-up: A policy will achieve its desired outcome only if it provokes the targeted response. The same policy measure can lead to different perceptions of 'windows of opportunity' among stakeholders and provoke different evolutionary trajectories (through unforeseen responses of individual actors and bandwagon effects) to exploit such 'windows of opportunity'.

For instance, consider the impact of loose IPR in the two countries. In India, a switch to a loose patent regime in 1972 was correctly perceived as a 'window of opportunity' to increase profits through the development of re-engineering capabilities. It did not lead the Indian firms to patent new processes in the Indian patent office en masse, but it forced them to look for new methods of production compatible with local resources and constraints, since the original method could not be copied. Thus, they developed technological capabilities required for 'duplicative imitation' and 'creative imitation' (Kale and Little, 2007).

When some firms made huge profits via the creation and commercialization of lower priced generics, a secondary 'bandwagon effect' was triggered within the market. In 'winner takes all' tournaments, often the incremental technological innovations continued, with a second or third innovator improving upon earlier re-engineered products and grabbing the market share yet again, lowering the prices even further and increasing consumer welfare. As a consequence, Indian drug producers faced continual gales of Schumpeterian technological competition in which only the most diversified or the most technologically competent firms could survive and the Indian pharmaceutical market became very dynamic and competitive.

In Brazil, without any form of IPR, all new products and processes could be freely imitated. However, this did not induce Brazilian firms to invest in acquiring reengineering skills. As a business strategy, it was more profitable to focus on the last stages of formulations that required little capital investment and technical skills rather than undertake the costly project of building manufacturing capabilities in all stages of drug production. Indeed, the Brazilian firms found it profitable to mimic the Western MNCs rather than compete with them. So they also imported raw materials, bulk drugs and API, focused simply on the commercialization process with special care being bestowed on advertising and marketing routines. Even when public research organizations developed new technologies and transferred them to the private sector at the laboratory or pilot scale, Brazilian firms were reluctant to invest resources to learn to scale up the process technology to a manufacturing level. And this reluctance continued to be exhibited despite the willingness of the Brazilian State to buy their products to meet social needs.

Such 'commercial logic' of Brazilian firms had a secondary effect on the innovation system; it pushed the public sector to become active and attend to the needs of the citizens. As mentioned previously, from the late 1990s, when industrial policy was geared to support the public health system, government laboratories developed generics and incremental innovations for the public sector pharmaceutical firms. Today, about twenty public laboratories, which are very active in national research programs, contribute to 10% of national production in terms of volume (Bermudez et al., 2004).

Unexpected impact of policy in catching up: Policy formulated for a particular purpose can provoke an unforeseen response both within the country and abroad. For instance, while loose IPR designed to facilitate accumulation of re-engineering skills had little impact in Brazil, the Generics Act promulgated in 1999, in the interest of public health and safety, had a tremendous impact on catching-up. Until the Generics act, like in other developing countries, three types of medicines were available in the Brazilian market: branded drugs, generics and similars[22]. From this date, however, the Brazilian government chose to discriminate against similars in order to improve drug quality and also to minimize competition through brand differentiation as the similars were sold under local brand names. This regulatory change pushed firms to switch to the production of generics from similars and in the process pushed them towards a technology based competition.

Similarly, the Generics Act in Brazil and 'Hatch-Waxman Act of 1984' in the U.S.A., which were not at all designed with the objective of promoting foreign firms, did exactly that. For astute Indian firms these regulatory changes opened up new 'window of opportunity' and contributed to their becoming multinationals.

5. Conclusions

From the start, our findings have confirmed some basic tenets of the evolutionary literature on catching-up in terms of technological change and industrial growth. The national environment and national system of innovation in combination with the responses of the actors concerned, determines the country-specific industrial trajectory in any sector, which is also path dependent. Public investment and State policy are at the heart of the catch-up process, but public investments alone will not yield desired outputs if the underlying set of scientific, technological, institutional and social capabilities is inadequate. Moreover, as Nelson (2008) points out an 'accumulation of scientific and technological capabilities' through investment in human and physical capital alone is not adequate for successful 'assimilation' of technologies requires effective institutions.

Beyond this, do the case studies yield any new insight on the processes of catching up? We propose three inferences by way of contribution to the catch-up literature on accumulation of industrial capabilities.

[22] Referred to earlier in p. 15.

Our case studies demonstrate that *radical regulatory changes* can create '*windows of opportunity*' (Soete, 1985) and generate positive externalities, in a way very similar to radical technological discontinuities. Thus, the origins of 'windows of opportunity' for the accumulation of technological capabilities need not always be associated with a technological discontinuity, as is usually considered in the catch-up literature. Indeed, in the pharmaceutical sector, regulatory changes related to industrial competition, IPR, drug safety or public health may also open up 'windows of opportunity'.

They also show that 'windows of opportunity' may or may not be exploited. Final outcomes are uncertain, unpredictable, endogenous phenomena. They are guided by the beliefs and expectations of the different economic actors in the innovation system, which play a very important role in technological capacity building.

Finally, the experience of India and Brazil prove that even accumulation of institutions and scientific and technological capabilities need not be sufficient for catching-up. In addition, the institutions must induce appropriate endogenous responses from the concerned stakeholders. In other words, there is a need to ensure 'perceived incentives' or conditions, which give rise to a set of expectations that lead stakeholders to take actions that support the desired outcome of policy. By their very definition, a system of appropriate incentives is necessarily ad-hoc, idiosyncratic and context-dependent.

Now developing countries are again facing a radical regulatory change, namely TRIPS. So the question is: will TRIPS open up new 'windows of opportunity' for some players from developing countries?

Let us understand that TRIPS imposes the same rules for participating in the technology race for all countries. However, developing countries have much less resources to allocate for the preparation of such a race. Moreover, the opportunity cost of each unit of money invested in the technology race is higher for developing countries, as compared to developed countries, because of higher poverty burdens. They also suffer from technology retard. Therefore, in winner takes all technology races of the post TRIPS era, chances of poor countries emerging as winners, are quite dim. Effectively, this might mean a return to the neoclassical framework, where policy and institutions have a minimal impact on catching-up and firms have to create their own 'windows of opportunity' through own R&D regardless of the environment. Then, in this new context, what recommendations can be made for State policy and firm strategy in pharmaceuticals?

Make policy design more rational: Given financial constraints, more than ever policy makers and other stakeholders in developing countries, have to interact to design policy that matches the expectations of the different stakeholders to the maximum extent possible. Only with more dialogue and explicit bargaining can there be fewer surprises and more coordinated development. This implies that the different stakeholders, in particular policy makers, have to get out of their ivory towers to interact more with one another and contribute to a policy formulation that induces the desired responses to the maximum extent possible. Here civic associations need to be particularly active to ensure that catching-up in the pharmaceuticals is also increasingly inclusive.

Invest in public research and improve its contribution to catching-up: The case studies highlight that investment in universities and public research is not only necessary to ensure pools of qualified labor and technology transfer to private firms, but also to create a vibrant public sector that can fill in crucial niches underserved by private firms whenever necessary. In countries, such as India, there is a real decline in the role of universities and public sector laboratories in the catching-up process in pharmaceuticals. Given the challenges of biotechnology (and now nanotechnology), the contribution of public institutions is more important than ever.

Build regulation handling capabilities: catching-up in terms of regulatory bureaucracy could also impinge on the accumulation of technological capabilities in the future. For instance, at present, in India, a lack of effective regulatory bureaucracy in patenting of new chemical entities or drugs is definitely an institutional problem. Therefore, Indian firms tend to seek EPO and USPTO patents, which are far most costly and risky propositions for developing country firms.

Explore options for international cooperation: A myriad of possibilities can open up with a strategic exploration of South-South and North-South cooperation to develop common R&D programs, a common patent granting body, cross-licensing agreements or sharing of patent pools.

Coming now to firm strategy, we propose two main recommendations.

Continue to reinforce comparative advantage in generics and soft innovations: Many developing countries have more qualified personnel or/and personnel who can be hired at cheaper rates. Therefore, possible secondary windows of opportunity may also open up while investing to create new generics or incremental innovations in terms of drug delivery, dosage, and software to complement an original innovation. Much will also depend on how flexibilities in TRIPS are exploited, for instance whether developing country firms can innovate 'around' a known molecule exploiting provisions that allow for patenting, if the efficiency of the drug is significantly improved.

Watch out for new opportunities: New or previously unexploited 'windows of opportunity' may contribute to further accumulation of technological capabilities. Some possibilities are new uses of old technology, traditional knowledge and traditional medicines[23]. Another black window of opportunity through which we cannot see through at present, is associated with new forms of collaboration that are emerging between Western MNCs and leading developing country firms.

To conclude, what is the future likely to hold for Indian and Brazilian pharmaceutical firms? At first glance, since Indian and Brazilian firms have accumulated basic technological and innovation capabilities, the future should only look rosy for them in terms of further catch-up. However, the rate of accumulation of innovation capabilities is unlikely to be as high as in the past and the pecking order between India and Brazil may change.

[23] In a future, the exploration and exploitation of the rich Brazilian biodiversity may offer new opportunities for national players to be part of the next generation of new drugs development one way or another (Fialho, 2009).

In terms of challenges, both Indian and Brazilian firms have a great technological retard in recombinant technology and new drug discovery skills; and in addition, Brazilian firm do not have manufacturing capabilities in API. Moreover, like all developing country firms, both Indian and Brazilian firms are simply strapped for money to invest in R&D capabilities and the market also does not generate enough incentives for firms to invest much in R&D. For instance, even the sum of the R&D expenditures of the top 11 companies in India in 2005-2006 was only $379 million, while that of Pfizer was almost 20 times more at $7440 million (Chaudhuri, 2007). Similarly, in Brazil, the overall R&D expenditure on pharmaceuticals in the country touched a low $125 million in 2005 (De Lemos Capanema, 2006). Finally, the opportunity cost of resource allocation to R&D may be amplified by the fact that both Indian and Brazilian firms have lost a lucrative source of profit with TRIPS. They can no longer earn second-innovator rents from reengineering branded drugs.

In the above context can India rise to the new challenge and one day create a blockbuster? As of now no Indian firm has patented a new chemical entity, and therefore their innovative achievements in the future will depend on how their individual R&D initiatives and their participation in the international division of labor with Western and Japanese MNCs on the latter's drug discovery projects bear fruit.

Can Brazil ever achieve complete backward integration? With its current scientific capabilities, the main problem in Brazil is the lack of funds to buy the equipment that would make the necessary research and its commercialization a worthwhile business proposition. This constraint is made doubly difficult as their main competitors, the MNCs, already exploit these economies of scale at a global level and export massively to the Brazilian market.

Will the Indian and Brazilian trajectory ever cross each other or will they be still divergent in future? Though nothing can be pronounced with certainty, some parameters which will play a role in determining the outcome can be identified. In India the innovation leaders in pharmaceuticals are the private sector firms, while in Brazil the public sector labs and firms are the motors of accumulation of innovative capacity. The competition will therefore be between private sector Indian firms and public sector Brazilian units (which will transfer technology to their firms).

The hotspots of the race will be in 'reengineering generics', 'creating incremental innovations' and 'learning from international technology alliances'. TRIPS has pushed the focus of innovation investment away from pure re-engineering to re-engineering of drugs that are off patent or will be off patent protection in the near future, i.e. generics. Firms of both countries are making forays into 'soft' innovations around new drugs, in terms of improvements in dosage, drug delivery, new uses for known molecules and cost reducing process innovations for generics. Again, firms in India and Brazil are collaborating with Western and Japanese MNCs in the upstream-labor intensive research segments and in the risky down-stream clinical trials and the returns are not yet clear. Currently India is in the lead in terms of reengineering of generics, creation of incremental innovations and initiation (and participation) in international technology alliances, but as Brazil builds capabilities in biotechnology, it is imminently possible that Brazil leapfrogs over India, unless the Indian public sector becomes more dynamic and public-private cooperation becomes more fruitful.

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